Missouri Department of Health & Senior Services

Health Alert

November 8, 2001

HA#29

FROM: **MAUREEN E. DEMPSEY, M.D.**
DIRECTOR

SUBJECT: **MMWR Weekly Report dated November 9, 2001/ Vol. 50/No. 44**

The Department of Health and Senior Services is forwarding the following information from CDC. Please contact the Department if you have any questions at 1-800-392-0272.

Attached are excerpts of the November 9 MMWR. These excerpts relate to investigation of bioterrorism-related anthrax and considerations for distinguishing influenza-like illness from inhalational anthrax.

The entire MMWR can be viewed at CDC's website at www.cdc.gov/mmwr/ or at the Department's website at www.dhss.state.mo.us.

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MISSOURI DEPARTMENT OF HEALTH AND SENIOR SERVICES dhss

FROM: **MAUREEN E. DEMPSEY, M.D.**
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SUBJECT: **UPDATE: INVESTIGATION OF BIOTERRORISM-RELATED ANTHRAX AND ADVERSE EVENTS FROM ANTIMICROBIAL PROPHYLAXIS (HA #29 ATTACHMENT)**

DATE: **NOVEMBER 8, 2001**

Excerpts from MMWR Vol. 50 No. 44

CDC and state and local public health authorities continue to investigate cases of bioterrorism-related anthrax. As of November 7, a total of 22 cases of anthrax have been identified according to the CDC surveillance case definition; 10 were confirmed inhalational anthrax cases and 12 cases (seven confirmed and five suspected) were cutaneous anthrax (Table 1). The majority of cases have occurred in persons working at postal facilities in New Jersey (NJ) and the District of Columbia (DC) in which letters contaminated with anthrax were handled or processed using high-speed sorting machines, or at media companies in New York City (NYC) or Florida (FL) where letters, either confirmed or presumed to be contaminated with anthrax, were opened or handled. The probable exposures for a case of cutaneous anthrax in NJ and a case of inhalational anthrax in NYC remain unknown. Epidemiologic investigations of these cases and surveillance to detect new cases of bioterrorism-associated anthrax continue. This report updates the investigation of these cases and describes adverse events associated with antimicrobial prophylaxis.

Since the last report (1), one additional case of confirmed cutaneous anthrax has been identified in a 38-year-old man who worked at a media company in NYC. This is the third case of cutaneous anthrax reported among employees at the media company and is probably associated with a contaminated letter postmarked September 18 that was handled during October 12–15. On October 23, the patient noted a small nonerythematous, nonpruritic, and painless lesion on his forehead. On October 28, a physician evaluated

TABLE 1. Number of cases of anthrax, by site — September–October 2001

Site	Florida	New York City	District of Columbia	New Jersey*	Total
Inhalational					
Confirmed	2	1	5	2	**10**
Suspected	0	0	0	0	**0**
Total	**2**	**1**	**5**	**2**	**10**
Cutaneous					
Confirmed	0	4	0	3	**7**
Suspected	0	3	0	2	**5**
Total	**0**	**7**	**0**	**5**	**12**

*Includes one case each from Pennsylvania and Delaware.

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the patient and described a lesion 1.4 cm in diameter, the center of which was depressed and dark gray; the same day, he was started on ciprofloxacin. A biopsy was positive for Bacillus anthracis by culture and immunohistochemical staining. No other new cases have been identified from investigations in FL, DC, NJ, NYC, or other areas.

Recommendations for antimicrobial prophylaxis to prevent inhalational anthrax have been directed by epidemiologic and laboratory findings. Approximately 300 postal and other facilities have been tested for B. anthracis spores and approximately 32,000 persons have initiated antimicrobial prophylaxis following potential exposure to B. anthracis at workplaces in FL, DC, NJ, and NYC. Clean-up at contaminated sites and surveillance for new anthrax cases are ongoing.

Adverse Events from Antimicrobial Prophylaxis

During October 8–10, a total of 1,132 persons from company A in Boca Raton, Florida, received initial antimicrobial prophylaxis for presumed exposure to B. anthracis; 970 (86%) persons received ciprofloxacin. After 14 days of prophylaxis, of 1,000 persons for whom information was available, 797 (80%) were still taking antibiotics.

A questionnaire was administered on approximately day 7 or day 14 of prophylaxis to assess adverse events in 490 (62%) persons who reported taking antibiotics. Of 490 persons, 95 (19%) reported one or more of the following symptoms: itching; breathing problems; swelling of face, neck, or throat; or seeking medical attention for any adverse events related to taking the antibiotic. Clinic record review and telephone interviews of the 95 indicated that six persons reported seeking medical attention and did not continue taking their original medication, possibly because of adverse events. A detailed questionnaire was administered to these six persons to determine the temporal association between initiation of antimicrobial prophylaxis and symptom onset, medical care received, and underlying illnesses. Two persons had been seen by a physician as outpatients, two had been seen in emergency departments, and two had been hospitalized. None of the persons had documented objective findings or clinical history attributable to adverse events, including anaphylaxis (2). Similar screening for adherence to and adverse events associated with antimicrobial prophylaxis has been initiated in DC, NJ, and NYC.

Public Health Response

CDC and local health departments continue to respond to public concern and bioterrorism threats. During October 8–31, CDC's Emergency Operations Center received 8,860 telephone inquiries from all 50 states, Puerto Rico, Guam, and 22 foreign countries. Of these, 590 (6.7%) calls were thought to represent a potential threat as defined by a report of exposure to a substance possibly associated with bioterrorism or symptoms consistent with an illness associated with bioterrorism. The 590 calls regarding potential threats were from physicians or other health-care workers (40%); local or state health departments (14%); private citizens (14%); and police, fire, or emergency response departments (7%). In response to the calls, CDC has provided information; referred to appropriate local, state, or federal agencies; assisted with clinical diagnosis or management; or initiated additional epidemiologic investigations of illnesses compatible with bioterrorism.

State and local public health agencies also are addressing public concerns and investigating potential bioterrorist threats. CDC has established a secured web-based system for states to report weekly summaries of their bioterrorism-related activities. For the week of October 21–27, Colorado, Connecticut, Louisiana, Maryland, Montana, North

Dakota, Tennessee, Wisconsin, and Wyoming reported 2,817 bioterrorism-related calls (mean per state: 313; range: 23–800) and approximately 25 investigations of bioterrorism threats in each state. From eight to 30 full-time personnel are engaged in these responses in each state.

For the same period, public health laboratories in 46 states participating in the Laboratory Response Network reported receiving approximately 7,500 specimens and isolates for B. anthracis testing. These specimens were primarily from environmental samples and nasal swabs.

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Editorial Note: Since the last report, one new case of confirmed cutaneous anthrax has been identified in a media company employee resulting from exposure to a previously known contaminated letter. The probable source of exposure for two cases reported last week (one cutaneous and one inhalational) has yet to be determined. Although these two cases ultimately might be attributed to letter handling, the lack of a discernable link to previous cases or workplaces raises the possibility of new routes of exposure or new target populations.

Since October 8, approximately 32,000 persons with potential exposure to B. anthracis in FL, NJ, NYC, and DC have initiated antimicrobial prophylaxis to prevent anthrax infection, and for approximately 5,000 persons, a 60-day course of antibiotics has been recommended. The Code of Federal Regulations* defines a serious adverse event associated with using a biologic product in humans as any of the following: death, life-threatening adverse event, inpatient hospitalization or prolongation of an existing hospitalization, persistent or substantial disability/incapacity, congenital anomaly/birth defect, or an important medical event that requires medical or surgical intervention to avert one of these outcomes. Although two persons were hospitalized in FL, their illnesses were not associated with antimicrobial prophylaxis. Efforts to contact persons who have not yet received followup are ongoing.

Adverse events associated with ciprofloxacin and doxycycline have been welldescribed among patients taking these medications for short-term treatment of bacterial infections. Anaphylactoid reactions caused by drug reaction have been reported rarely (3). However, few data exist regarding the use of these antimicrobials for longer periods. Because many persons are receiving antimicrobial prophylaxis, enhanced surveillance programs are essential to detect and monitor adverse events associated with these medications. Moreover, these programs will monitor adherence to the full 60-day regimen, enabling the design of better programs to promote completion of recommended prophylactic regimens.

CDC and state and local public health agencies are continuing epidemiologic and laboratory investigations of bioterrorism-related anthrax. Even without confirmed cases of anthrax, state and local health departments have responded to public concerns and

* 21 CFR 600.80.

have applied substantial personnel and laboratory resources to address anthrax issues in recent weeks. Recent cases of anthrax are attributed to intentional infection of persons and represent criminal acts that are being investigated by federal law enforcement agencies. Because new cases of anthrax may occur, public health authorities and clinicians should remain vigilant.

References
1. CDC. Update: investigation of bioterrorism-related anthrax and interim guidelines for clinical evaluation of persons with possible anthrax. MMWR 2001;50:941–8.
2. Neugut AI, Ghatak AT, Miller RL. Anaphylaxis in the United States. Arch Intern Med 2001;161:15–21.
3. Davis H, McGoodwin E, Reed TG. Anaphylactoid reactions reported after treatment with ciprofloxacin. Ann Int Med 1989;111:1041–3.

Notice to Readers

Considerations for Distinguishing Influenza-Like Illness from Inhalational Anthrax

CDC has issued guidelines on the evaluation of persons with a history of exposure to Bacillus anthracis spores or who have an occupational or environmental risk for anthrax exposure (1). This notice describes the clinical evaluation of persons who are not known to be at increased risk for anthrax but who have symptoms of influenza-like illness (ILI). Clinicians evaluating persons with ILI should consider a combination of epidemiologic, clinical, and, if indicated, laboratory and radiographic test results to evaluate the likelihood that inhalational anthrax is the basis for ILI symptoms.

ILI is a nonspecific respiratory illness characterized by fever, fatigue, cough, and other symptoms. The majority of ILI cases is not caused by influenza but by other viruses (e.g., rhinoviruses and respiratory syncytial virus [RSV]), adenoviruses, and parainfluenza viruses). Less common causes of ILI include bacteria such as Legionella spp., Chlamydia pneumoniae, Mycoplasma pneumoniae, and Streptococcus pneumoniae. Influenza, RSV, and certain bacterial infections are particularly important causes of ILI because these infections can lead to serious complications requiring hospitalization (2–4). Yearly, adults and children can average one to three and three to six ILI, respectively (5).

Epidemiologic Considerations

To date, 10 confirmed cases of inhalational anthrax have been identified (1). The epidemiologic profile of these 10 cases caused by bioterrorism can guide the assessment of persons with ILI. All but one case have occurred among postal workers, persons exposed to letters or areas known to be contaminated by anthrax spores, and media employees. The 10 confirmed cases have been identified in a limited number of communities. Inhalational anthrax is not spread from person-to-person. In comparison, millions of ILI cases associated with other respiratory pathogens occur each year and in all communities. Respiratory infections associated with bacteria can occur throughout the year; pneumococcal disease peaks during the winter, and mycoplasma and legionellosis are more common during the summer and fall (4). Cases of ILI resulting from influenza and RSV infection generally peak during the winter; rhinoviruses and parainfluenza virus infections usually peak during the fall and spring; and adenoviruses circulate throughout the year. All of these viruses are highly communicable and spread easily from person to person.

Clinical Considerations

Although many different illnesses might present with ILI symptoms, the presence of certain signs and symptoms might help to distinguish other causes of ILI from inhalational anthrax. Nasal congestion and rhinorrhea are features of most ILI cases not associated with anthrax (Table 1) (6,7). In comparison, rhinorrhea was reported in one of the 10 persons who had inhalational anthrax diagnosed since September 2001. All 10 persons with inhalational anthrax had abnormal chest radiographs on initial presentation; seven had mediastinal widening, seven had infiltrates, and eight had pleural effusion. Findings might be more readily discernable on posteroanterior with lateral views, compared with anteroposterior views (i.e., portable radiograph alone) (1). Most cases of ILI are not associated with radiographic findings of pneumonia, which occurs most often

TABLE 1. Symptoms and signs of inhalational anthrax, laboratory-confirmed influenza, and influenza-like illness (ILI) from other causes

Symptom/Sign	Inhalational anthrax (n=10)	Laboratory-confirmed influenza	ILI from other causes
Elevated temperature	70%	68%–77%	40%–73%
Fever or chills	100%	83%–90%	75%–89%
Fatigue/malaise	100%	75%–94%	62%–94%
Cough (minimal or nonproductive)	90%	84%–93%	72%–80%
Shortness of breath	80%	6%	6%
Chest discomfort or pleuritic chest pain	60%	35%	23%
Headache	50%	84%–91%	74%–89%
Myalgias	50%	67%–94%	73%–94%
Sore throat	20%	64%–84%	64%–84%
Rhinorrhea	10%	79%	68%
Nausea or vomiting	80%	12%	12%
Abdominal pain	30%	22%	22%

among the very young, elderly, or those with chronic lung disease (2,3). Influenza associated pneumonia occurs in approximately 1%–5% of community-dwelling adults with influenza and can occur in >20% of influenza-infected elderly (2). Influenza-associated pneumonia might be caused by the primary virus infection or, more commonly, by bacterial infection occurring coincident with or following influenza illness (2).

Testing

No rapid screening test is available to diagnose inhalational anthrax in the early stages. Blood cultures grew B. anthracis in all seven patients with inhalational anthrax who had not received previous antimicrobial therapy. However, blood cultures should not be obtained routinely on all patients with ILI symptoms who have no probable exposure to anthrax but should be obtained for persons in situations in which bacteremia is suspected.

Rapid tests for influenza and RSV are available, and, if used, should be conducted within the first 3–4 days of a person's illness when viral shedding is most likely. RSV antigen detection tests have a peak sensitivity of 75%–95% in infants but do not have enough sensitivity to warrant their routine use among adults (8).

Among the influenza tests available for point-of-care testing, the reported sensitivities and specificities range from 45%–90% and 60%–95%, respectively (9). Two tests

(Quidel Quickvue Influenza test and ZymeTx Zstatflu test®) can be performed in any physician's office, and three are classified as moderately complex tests (Biostar FLU OIA; Becton-Dickinson Directigen Flu A + B; and Becton-Dickinson Directigen Flu A™).

The clinical usefulness of rapid influenza tests for the diagnosis of influenza in individual patients is limited because the sensitivity of the influenza rapid tests is relatively low (45%–90%), and a large proportion of persons with influenza might be missed with these tests. Therefore, the rapid influenza tests should not be done on every person presenting with ILI. However, rapid influenza testing used with viral culture can help indicate whether influenza viruses are circulating among specific populations, (e.g., nursing home residents or patients attending a clinic). This type of epidemiologic information on specific populations can aid in diagnosing ILI.

Vaccination against influenza is the best means to prevent influenza and its severe complications. The influenza vaccine is targeted towards persons aged >65 years and to persons aged 6 months to 64 years who have a high risk medical condition because these groups are at increased risk for influenza-related complications. The vaccine also is targeted towards health-care workers to prevent transmission of influenza to high-risk persons. In addition, vaccination is recommended for household members of high-risk persons and for healthy persons aged 50–64 years. The vaccine can prevent 70%–90% of influenza infections in healthy adults. However, the vaccine does not prevent ILI caused by infectious agents other than influenza, and many persons vaccinated against influenza will still get ILI. Therefore, receipt of vaccine will not definitely exclude influenza from the differential diagnosis of ILI or increase the probability of inhalational anthrax as a cause, especially among persons who have no probable exposure to anthrax. Frequent hand washing can reduce the number of respiratory illnesses (10) and pneumococcal polysaccharide vaccine can reduce the risk for serious pneumococcal disease.

Additional information about anthrax is available at <http://www.hhs.gov/hottopics/healing/biological.html> and <http://www.bt.cdc.gov/DocumentsApp/FactsAbout/FactsAbout.asp>. Additional information about influenza, RSV and other viral respiratory infections, and pneumococcal disease is available at <http://www.cdc.gov/ncidod/diseases/flu/fluvirus.htm>, <http://www.cdc.gov/nip/flu/default.htm>, <http://www.cdc.gov/ncidod/dvrd/revb/index.htm>, <http://www.cdc.gov/ncidod/dbmd/diseaseinfo/streppneum_t.htm>, and <http://www.cdc.gov/nip/diseases/Pneumo/vac-chart.htm>.

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lower respiratory tract specimens suspected of containing the respiratory syncytial virus. Arch Pathol Lab Med 1991;115:451–8.
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Notice to Readers

Interim Guidelines for Investigation of and Response to Bacillus Anthracis Exposures

Environmental Sampling. Environmental testing to detect B. anthracis on surfaces or in the air can be used to investigate known or suspected exposure events. The highest priority of an investigation is to evaluate the risk for exposure to aerosolized B. anthracis spores. Persons collecting and testing samples should 1) obtain adequate samples, 2) avoid cross-contamination during processing, and 3) ensure proficient laboratory testing and interpretation of test results. A positive laboratory test for B. anthracis from a sample of an environmental surface may be caused by cross-contamination from an exposure vehicle (e.g., contact with an envelope containing B. anthracis), background occurrence of B. anthracis spores in the environment, or previously aerosolized B. anthracis that has settled onto environmental surfaces. Laboratory test results of environmental surface samples should not be the only criterion for starting, continuing, or stopping antimicrobial prophylaxis for inhalational disease.

Environmental sampling can be directed, prospective, or random. In directed sampling, air and/or surface samples are obtained as part of an investigation of a specific threat, a known exposure, or of persons with bioterrorism-related anthrax. Directed environmental sampling may play a critical role in characterizing potential exposures and guiding public health action (Box 1).

Prospective environmental sampling is defined as ongoing sampling and testing of air or surfaces for B. anthracis spores. The value of prospective sampling is not known. Current technologies for monitoring air for B. anthracis and other agents are not validated and their performance has not been assessed during bioterrorism events. Prospective environmental sampling of surfaces may have a role in detecting B. anthracis contamination, especially at facilities or events determined to be at high risk for bioterrorism (Box 1).

The testing of random environmental samples (i.e., sampling air or surfaces of facilities that are not directly associated with confirmed anthrax disease or a known B. anthracis exposure) is of uncertain utility in detecting past exposures. Random positive tests for B. anthracis spores may represent cross-contamination from an exposure vehicle (e.g., letter) that poses negligible risks for inhalational anthrax. These positive test results may prompt more extensive evaluation to direct cleanup, if needed.

Nasal Swab Cultures. Nasal swab cultures should not be used to diagnose cases of anthrax or to evaluate whether a person had been exposed. Nasal swab cultures may be useful in the investigation of known or suspected airborne B. anthracis (Box 1). Because the sensitivity of nasal swab cultures decreases over time, cultures should be obtained within 7 days of the exposure. The presence of B. anthracis from a nasal swab culture cannot be determined by gram stain or colony characteristics alone and requires confirmatory testing by qualified laboratories.

Antimicrobial Prophylaxis. Antimicrobial prophylaxis is used to prevent cases of inhalational anthrax (Box 1). Public health authorities often start prophylaxis before the extent of exposure is known. Subsequent epidemiologic and laboratory test data may indicate that some persons started on prophylaxis were not exposed. These persons should stop antimicrobial prophylaxis. Persons who were exposed should complete 60

Box 1

BOX 1. Interim guidelines for investigation of and response to *B. anthracis* exposures

Environmental Sampling

Directed sampling of environmental surfaces may be indicated:

- To identify a site or source of *Bacillus anthracis* exposure that has resulted in a case(s) of anthrax
- To trace the route of an exposure vehicle (e.g., a powdercontaining letter)
- To obtain the *B. anthracis* strain when isolates from patients are not available
- To guide cleanup activities in a contaminated area or building
- To assess biosafety procedures in laboratories processing *B. anthracis* specimens

Prospective sampling of environmental surfaces may be indicated:

- To identify receipt of a contaminated exposure vehicle in high risk facilities (e.g., mailrooms of targeted persons or groups)
- To detect aerosolized *B. anthracis* in high risk areas or events

Laboratory testing of environmental surface samples should not be the only means to determine the need for antimicrobial prophylaxis.

Nasal Swab Cultures

Collection of nasal swabs for culture of *B. anthracis* may be useful:

- To help define an area of exposure to aerosolized *B. anthracis*
- To help ascertain where a person with inhalational anthrax was exposed if the time and place of exposure are not already known

Collection of nasal swabs for culture of *B. anthracis* is not indicated:

- To diagnose anthrax
- To determine a person's risk of exposure and the need for antimicrobial prophylaxis
- To determine when antimicrobial prophylaxis should be stopped
- To supplement random environmental sampling

Antimicrobial Prophylaxis

Antimicrobial prophylaxis may be initiated pending additional information when:

- A person is exposed to an air space where a suspicious material may have been aerosolized (e.g., near a suspicious powder-containing letter during opening)
- A person has shared the air space likely to be the source of an inhalational anthrax case

Antimicrobial prophylaxis should be continued for 60 days for:

- Persons exposed to an air space known to be contaminated with aerosolized *B. anthracis*
- Persons exposed to an air space known to be the source of an inhalational anthrax case
- Persons along the transit path of an envelope or other vehicle containing *B. anthracis* that may have been aerosolized (e.g., a postal sorting facility in which an envelope containing *B. anthracis* was processed)
- Unvaccinated laboratory workers exposed to confirmed *B. anthracis* cultures

Box 1 continued

Antimicrobial prophylaxis is not indicated:

- For prevention of cutaneous anthrax
- For autopsy personnel examining bodies infected with anthrax when appropriate isolation precautions and procedures are followed
- For hospital personnel caring for patients with anthrax
- For persons who routinely open or handle mail in the absence of a suspicious letter or credible threat

A positive test for B. anthracis from a randomly collected specimen does not require implementation of antimicrobial prophylaxis or the closing of a facility.

Closing a Facility

Closing a facility or a part of a facility may be indicated:

- After an inhalational anthrax case is detected and a probable site of exposure in the facility is identified
- When there is a known aerosolization of *B. anthracis* in the facility
- When evidence strongly suggests an aerosolization of *B. anthracis* in the facility
- As determined by law enforcement authorities in a criminal investigation

Closing a facility is not indicated:

- Based only on the identification of *B. anthracis* from samples of environmental surfaces
- Based only on the identification of a cutaneous anthrax cases

days of therapy. No shorter course of antimicrobial prophylaxis exists. The choice of an antimicrobial agent should be based on antimicrobial susceptibility, the drug's effectiveness, adverse events, and cost. B. anthracis isolates from patients with bioterrorism-related anthrax have been susceptible to ciprofloxacin, doxycycline, and other agents; the use of doxycycline may be preferable to prevent development of ciprofloxacin resistance in more common bacteria (1). Respiratory transmission of B. anthracis from person-to-person does not occur; no antimicrobial prophylaxis is indicated.

Closing Facilities. The decision to close a facility is made to prevent cases of inhalational anthrax (Box 1). The facility should remain closed until the risk for inhalational disease is eliminated.

Reference

1. CDC. Update: investigation of bioterrorism-related anthrax and interim guidelines for exposure management and antimicrobial therapy, October 2001. MMWR 2001;50:909–19.